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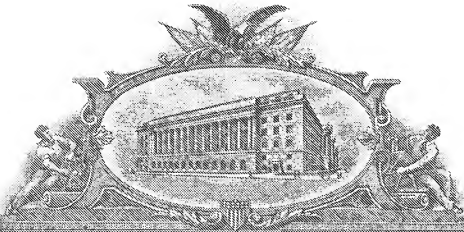
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## PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV 381773108 US

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Additional inventors are being named on the <u>2nd pg</u> separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
A REAGENT DELIVERY SYSTEM AND A STAINING APPARATUS FOR PROCESSING BIOLOGICAL SAMPLES AND A REAGENT DISPENSING DEVICE AND A REAGENT CONTAINER FOR USE IN SUCH DELIVERY SYSTEMS					
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ENCLOSED APPLICATION PARTS (check all that apply)					
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<input checked="" type="checkbox"/> Drawing(s) Number of Sheets <u>15</u>		<input checked="" type="checkbox"/> Other (specify) Power of Attorney, Transmittal Letter, Certificates of Express Mail & postcard			
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METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT					
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.		FILING FEE Amount (\$)			
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[Page 1 of 2]

Respectfully submitted,

SIGNATURE Nicole A. Ressue

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Date March 2, 2004

REGISTRATION NO. 48,665

(if appropriate)

Docket Number: DakoCytoProbe-P118

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Docket Number EV 381773108 US

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[Page 2 of 2]

Number 2 of 2

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Express Mail No.: EV 381773108 US  
Attorney Docket: DakoCytoProbe-P118

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UNITED STATES PATENT AND  
TRADEMARK OFFICE

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In Re the Provisional Application of: John Favuzzi, Kristopher Buchanan, Merritt M. Martin, Jr.,  
Loren Bland, Jonathan Sweda, Robert Lathrop, John Van  
Bosch

Serial Number:

Filed:

For: A Reagent Delivery System and A Staining Apparatus For Processing  
Biological Samples and A Reagent Dispensing Device and A Reagent  
Container for Use in Such Delivery Systems

Assignee: DakoCytomation Denmark A/S

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LETTER OF TRANSMITTAL

Mail Stop Provisional Patent Application  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

Enclosed for filing are:

1. a Provisional Application Cover Sheet (2 pages);
2. an Application Data Sheet (5 pages);
3. a Power of Attorney (2 pages);
4. a Specification (37 pages) and Drawings (15 pages);
5. this Letter of Transmittal (2 pages) along with a Credit Card Payment Form authorization (1 page) in the amount of \$160.00 for the provisional filing fee;
6. Certificates of Express Mailing for each document and a return postcard.

Please confirm receipt of the documents by applying your date stamp on the enclosed postcard receipt and returning it to me.

**Please address all future correspondence to: Santangelo Law Offices, P.C., 125 South Howes, Third Floor, Fort Collins, CO 80521.**

I have this 2<sup>nd</sup> day of March, 2004, either myself personally or through my direction of staff at this office, deposited all of the items in the above letter of transmittal with the United States Postal Service as Express Mail, postage prepaid, in an envelope addressed to: Mail Stop Provisional Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated this 2 day of March, 2004.

Respectfully Submitted,  
SANTANGELO Law Offices, P.C.

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UNITED STATES PATENT AND  
TRADEMARK OFFICE

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In Re the Provisional Application of: John Favuzzi, Kristopher Buchanan, Merritt M. Martin, Jr.,  
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For: A Reagent Delivery System and A Staining Apparatus For Processing  
Biological Samples and A Reagent Dispensing Device and A Reagent  
Container for Use in Such Delivery Systems

Assignee: DakoCytomation Denmark A/S


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**CERTIFICATE OF EXPRESS MAILING**

I, Brittney L. Swensen, hereby certify to the truth of the following items:

1. I am an employee of Santangelo Law Offices, P.C., 125 South Howes, Third Floor, Fort Collins, Colorado 80521.
2. I have this day deposited the attached Provisional Application Cover Sheet (2 pages) with the United States Postal Service as "Express Mail" for mailing to Mail Stop Provisional Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated this 2<sup>nd</sup> day of March, 2004.

  
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Brittney L. Swensen

A REAGENT DELIVERY SYSTEM AND A STAINING APPARATUS FOR PROCESSING BIOLOGICAL SAMPLES AND A REAGENT DISPENSING DEVICE AND A REAGENT CONTAINER FOR USE IN SUCH DELIVERY SYSTEMS

5 TECHNICAL FIELD

The invention relates to a reagent delivery system in an apparatus for processing biological samples arranged on carrier elements, and a staining apparatus for processing biological samples as well as a reagent-dispensing device and a reagent container for use in such delivery systems and apparatus. The invention further  
10 relates to a method of aspirating and dispensing reagents

Reagent delivery systems may be used in an automated sample processing apparatus, such as staining apparatus, for treating samples arranged on carrier means, such as microscope slides or sample tubes, located at predefined positions  
15 close to or in the apparatus by aspirating a portion of selected reagent from a station containing a plurality of reagents and thereafter dispense the reagent to a sample, e.g. a tissue, organic cells, bacteria etc., arranged on the carrier means. The invention facilitates the aspiration and dispensing of reagents.

20 BACKGROUND OF INVENTION

Staining apparatuses for staining and treating samples by means of probes normally comprises a first station for containing one or more reagent vials; a second station for mounting slides, a probe arranged to aspirate a portion of reagent from a selected reagent vial and dispensing the reagent to a slide on which the sample is  
25 arranged and a drive means for moving the probe between the various stations.

A sample is in this application to be understood as a biological sample such as histological samples, e.g. tissue and cell specimens, including cell lines, proteins and synthetic peptides, tissues, cell preparations, blood, bodily fluids, bone marrow,  
30 cytology specimens, blood smears, thin-layer preparations, and micro arrays, and specifically biological samples on microscope slides.



The term staining is used for the end product of the process, by which certain parts of the sample may be stained, i.e. have obtain a different colour, either in the optic range or in another electromagnetic range, such as ultra violet, or the staining may be an detectable, preferably automatically detectable, change in properties, such as fluorescent properties, magnetic properties, electrical properties or radioactive properties. To obtain the staining, the sample normally have to undergo a series of treatment steps, such as but not limited to; washing, binding of reagents to the specific parts of the sample, activation of the reagents, etc. and each treatment step may include a plurality of individual treatments.

10

The vial station is a collection of a plurality of vials, at least two but often 20-60 vials or more, which may or may not be physically arranged in close proximity to each other. The term station does not indicate that the vials must be located within one, confined area; rather it indicates the existence of a plurality of vials. The probe drive means may be a robot arm with two or three degrees of freedom, such as an articulated arm or one track or a set of perpendicular tracks along which a probe retainer of the probe drive means may be displaced, wherein the probe retainer may be moved in a direction normal to the track or tracks. The skilled person may readily design other types of probe drive means, e.g. combinations of the above described.

20

The carrier means may be provided to the apparatus in a two-dimensional array, e.g. constituted by individual rows of carrier means as discussed in the example below, or the carrier means may be provided in any manner known in the art, e.g. arranged in a carrousel or as a row of carrier means. The carrier means may also be arranged movably with respect to the probe drive means, such as in an endless row that is advanced automatically past the operating area of the probe drive means or as a two-dimensional array that may be moved in a direction perpendicular to a travel direction of the probe drive means, so that the probe may reach any carrier means by the combined movement of the probe and the array.

30

The carrier means are preferably arranged in groups or series on trays or the like, so that a plurality of carrier means may be removed from or situated in the apparatus simultaneously, and the apparatus preferably also comprises means for

performing the intermediate storage of the carrier means with samples thereon and the removal of the carrier means from the apparatus automatically.

- The operation of the staining apparatus will generally be controlled by means of
- 5 control means, typically a computer having a central processing unit and one or more memory unit associated therewith, means for controlling the various operations of the apparatus by controlling step motors, solenoids, valves and/or other drive or control parts of the apparatus. The control means may have one or more data communication ports for enabling data communication with external
- 10 computers by wire or wireless. The control means does not have to be physically arranged within the apparatus itself but may be a computer external to the staining apparatus and connected to the apparatus via a data transmission port thereof.

- Applications to which the present invention may especially relate include
- 15 immunohistochemistry, in-situ hybridization, fluorescent in-situ hybridization, special staining, and cytology, as well as potentially other chemical and biological applications.

- Sample processing in immunohistochemical (IHC) applications and in other
- 20 chemical and biological analyses may require one or a number of various processing sequences or protocols as part of an analysis of one or more samples. The sample processing sequences or protocols may be defined by the individual or organization requesting an analysis, such as a pathologist or histologist of a hospital, and may be further defined by the dictates of a particular analysis to be
- 25 performed.

- In preparation for sample analysis, a biological sample may be acquired by known sample acquisition techniques and may comprise, for example in IHC applications, tissues generally or even in some applications one or a plurality of isolated cells,
- 30 such as in microarray samples, and may be presented on a sample carrier such as a microscope slide. Furthermore, the sample may be presented on the carrier variously and potentially in some form of preservation. As one example, a sample

such as a layer or slice of skin may be preserved in formaldehyde and presented on a carrier with one or more paraffin or other chemical layers infiltrating the sample.

- Immunologic and histological applications, for example, may require processing sequences or protocols that comprise steps such as deparaffinization, target retrieval, and staining, especially for in-situ hybridization (ISH) techniques. Previously, in some applications, these steps may have been performed manually, potentially creating a time-intensive protocol and necessitating personnel to be actively involved in the sample processing. Attempts have been made to automate sample processing to address the need for expedient sample processing and a less manually burdensome operation. However, such previous efforts may have not fully addressed the needs for an automated sample processing system. Previous efforts to automate sample processing may be deficient in several aspects that prevent more robust automated sample processing, such as: the lack of sufficient computer control and monitoring of sample processing; the lack of information sharing for processing protocol and processing status, especially for individual samples; the lack of diagnostic capabilities; and the lack of real-time or adaptive capabilities for multiple sample batch processing.
- Past efforts at automated sample processing for samples presented on carriers such as slides, such as US Patent No. 6352861 to Ventana Medical Systems, Inc. and US Patent No. 5839091 to LabVision Corporation, have not afforded the various advantages and other combinations of features as presented herein.
- US-A-5,948,359 discloses an apparatus of the above mentioned type, wherein the first station comprises a vial holder for holding 40 or more vials in order to provide a wide range of different reagents adapted for different staining purposes, and thereby the possibility of automatically staining a large number of slides requiring different staining processes. In practise it is very important that the apparatus facilitates that many different staining processes can be performed at the same time in the apparatus, because this avoids the necessity of batching samples requiring the same procedure or other treatment with reagents, and processing each batch individually.

US-A-5,839,091 discloses a staining apparatus and a method of the above-mentioned kind, said apparatus comprising a reagent probe assembly for applying reagents onto a slide and the probe is washed between the individual reagent applications in a wash station.

5

US 6,537,818 discloses a system and method of aspirating and dispensing reagent Also US 2003/0194349; US 6,498,037; US 6,436,349; US 5,213,764, US 4,869,114; and US 3,960,020 show probes dispensing reagents.

- 10 An object by the present invention is to provide a reagent delivery system for a sample processing apparatus and a probe assembly therefore wherein the accuracy of dispensed volumes and the throughput is better than hereto known.

Further objects of the present invention are to improve the known apparatuses for staining samples as well as the method for automatic staining of samples by

- 15 facilitating a wider range of available processes of treatment, so as to increase the number of different staining and/or treatment processes that may be performed automatically, alternatively or additionally to provide an increased quality of some specific staining processes.

## 20 SUMMARY OF THE INVENTION

The invention provides a reagent delivery system in an apparatus for processing biological samples arranged on carrier elements, the apparatus comprising a stationary reagent section having one or more reagent containers and a stationary  
25 staining section in which at least one carrier element is arranged; and wherein the reagent delivery system comprises a probe for aspirating a portion of reagent from a reagent container in order to dispense a predetermined amount on a predetermined carrier element, a probe handling device for handling the probe; wherein the probe comprises a continuous probe tubing (101) extending through a rigid probe member (102) and providing fluid communication from a dispensing end (104) of said probe member to a pneumatic pressure regulation device and wherein the rigid probe member is adapted for cooperation with the closure of the reagent container.

30

This structure enables a fast operation with a very little carry-over as the probe is easy to clean since there are no assembled parts along the inner side of the probe.

Further In order to support a fast operation a plurality of probes such as two, three or four probes may be provided in order to allow for dispensing different reagent without washing the probe between each dispensing.

- 5    The rigid probe member may be arranged to cooperate with at least one reagent container in such manner that the probe may penetrate an opening covered by cap comprising a septum, aspirate reagent, and withdraw from the container, and wherein the septum may be adapted to regenerate as an almost tight closure of the reagent container, i.e. become substantially closed again. This is advantageous as
- 10 the probe can easily get access to the content in the reagent container. No time is wasted on removing caps and yet the reagents will be protected against evaporation and contaminations thanks to the ability of the septum to regenerate as an almost tight closure.
- 15 In a preferred embodiment the septum comprises a plurality of sectors, e.g. four sectors, such as flaps, which are free to flex upwards or downwards thereby allowing the aspirating end of the probe to penetrate the closure and the closure to almost regain its closed form after retraction of the probe.
- 20 Preferably the septum comprises a plurality of sectors, e.g. four sectors, such as flaps, which originally are connected by lines of weakness, and wherein the lines of weakness will break the first time a probe is inserted into the reagent container, and afterwards are free to flex upwards or downwards thereby allowing the aspirating end of the probe to penetrate the closure and the closure to almost regain its closed
- 25 form after retraction of the probe.

Preferably the dispensing end of the probe is a cone in order to facilitate the penetration through the septum in the closure of the reagent container.

- 30 Preferably a reagent container is provided with an identification, and the probe handling device comprises a robotic device also comprising a sensor element able to acquire information from the identification on the reagent container, and the robotic device is connected to a computer receiving the acquired information. Such identification enables the computer system controlling the reagent delivery in an

automated stainer to obtain information about the reagent containers located in the reagent section of the apparatus. In this manner it is possible to check that the reagent delivery system is aspirating the prescribed reagent.

- 5     The invention also provides a staining apparatus for automated processing of biological samples arranged on carrier elements, comprising a reagent section comprising one or more reagent containers; a staining section in which at least one carrier element is arranged; a reagent dispensing device for dispensing a portion of reagent onto a predetermined carrier element, a handling device for handling said
- 10    reagent dispensing device; wherein the reagent dispensing device comprises a continuous probe tubing extending through a rigid probe member and providing fluid communication from a dispensing end of said probe member to a pneumatic pressure regulation device.
- 15    The pneumatic pressure regulation device may include a vacuum source with which the tubing may communicate via a valve device. Preferably said valve device is operable to provide a predetermined pressure in the tubing in order to aspirate or dispense a predetermined amount of reagent at the dispensing end of the tubing. By controlling the pressure inside the tubing, the aspiration and dispensing of fluids
- 20    may be accurately controlled. By using pneumatic means for operating the probe tubing, the available reagent in the reagent containers as well as the available volume in the probe tubing may be fully exploited as reagent may be withdrawn from the reagent containers by applying vacuum to the tubing.
- 25    In a preferred embodiment the handling device includes a holder for holding the probe member; and a robotic motion system for moving the reagent dispensing device between predetermined locations relative to the carrier element and the reagent containers. The reagent dispensing device may be moved by a computer controlled robotic system able to direct the device to a specific reagent container for
- 30    aspirating a volume of reagent and to move on to a specific microscope slide to dispense the volume of reagent on the slide.

In a preferred embodiment of the probe the internal diameter of the tubing is between 1.0 mm and 2.0 mm, preferably between 1.2 mm and 1.8 mm and more

- preferably between 1.4 mm and 1.6 mm, such as about 1.5 mm (1/16 inch). The internal diameter is chosen so that the aspirated volume of reagent can be withheld in the tube. Further the narrow tube allow for a plurality of aspirated volumes separated by air bubbles aspirated between each volume of reagent. Aspirating a plurality of volumes for a plurality of microscope slides is very time-saving, supporting a high through-put of the apparatus, as the probe only moves once from reagent section to the staining section with the slides.

- The length of the tubing may be between 0.5 m and 2.5 m, preferably between 1.0 m and 2.0 m and more preferably between 1.3 m and 1.7 m, such as about 1.5 m. The length is advantageous for the ability to aspirate a plurality of volumes of reagents. Accordingly the length support a high through-put of the apparatus

- In a preferred embodiment the continuous tubing is provided with a spirally wound probe tubing section. This is advantageous for accommodation of the long thin tubing. Further the spiral section provides for the flexibility required when the probe is moved up or down. This is advantageous as the opposite end of the long tubing stays permanently connected to the pneumatic system.

- In the preferred embodiment the spirally wound probe tubing section is a coiled section. The coiled section may comprise at least one winding, and preferably between 5 and 30 windings, more preferably between 10 and 25 windings, and most preferably between 15 and 22 windings, such as 20 windings.

- The staining apparatus may comprise a washing station for cleaning the reagent-dispensing device. The valve device may further be adapted to provide a connection to a fluid source providing a wash solution or cleaning fluid for washing and or rinsing the probe tubing. Preferably the washing station comprises a receptacle (wash sump) able to accommodate a substantial portion of the dispensing end of the probe, and an outlet to waste, and the outlet to the waste may be located a distance above the bottom of the receptacle so that the wash fluid ejected from the dispensing end of the probe will wash the outer surface of the dispensing end of the probe before the wash fluid is drained to waste. Accordingly the probe can be washed in a fast and effective manner inside as well as outside in

a single process. After the wash the probe may be dried by air supplied to the tubing through the valve device. The washing fluid may be selectable from a plurality of fluids according to the tube cleaning requirements.

- 5 In a staining apparatus according to the invention the reagent section comprises a reagent rack providing a plurality of compartments for a plurality of reagent containers or container assemblies and wherein the cross-section of a compartment cooperates with the cross-section of the container or container assembly. The cross-section may be an unsymmetrical polygon, such as a rectangle with one corner-  
10 section replaced by a slanted/oblique fifth side.

- In a staining apparatus according to the invention a top wall of a reagent container is provided with a label comprising information identifying e.g. type of reagent, container volume size, date of delivery, date of end of use, and wherein the robot  
15 head further comprises an optical sensor, able to provide the information on the label to a computer system. These features are essential to the operation of the automated staining apparatus, in order to enable thorough control of the application of the prescribed reagent to the specified slide. A control system may include software for registering and tracking different relevant data and control the robotic  
20 movements and the washing action in accordance with a predetermined staining protocol transmitted to the control system.

- In a preferred embodiment an electrically conducting member of the reagent dispensing device is connected to an electronic circuit adapted for capacitive level  
25 sensing. (having ability to detect the reagent level by sensing an electrical capacity, and adapted to forward information about the detected level to the computer system). –Further the computer system may be adapted to issue an order for a new delivery of the reagent if the level is below a predetermined limit.

- 30 In a preferred embodiment wherein the computer system is connected to a plurality of staining apparatus, and further uses the reagent dispensing device to detect the level of reagent fluid in each reagent container, a controlling program is adapted to let the robotic system with the level sensor and the optical sensor update information about the available amount of reagent in the reagent containers in the



plurality of staining apparatus before starting a staining procedure, and is further adapted to recommend to an operator that a tissue slide requiring a specific reagent, be processed in a staining apparatus having a reagent container comprising the necessary volume of such specific reagent.

5

The invention provides a reagent dispensing device for use in a staining apparatus for processing of biological samples arranged on carrier elements, said device comprising a probe member having an aspirating and dispensing end, through which reagent may be aspirated and dispensed, and a mounting end; and wherein a  
10 continuous probe tubing is provided inside the probe member, said tubing extending from the aspirating and dispensing end through the entire probe member to pneumatic pressure regulation device. Such probe is easy to wash and carry-over is minimised as there is no assembled parts in the inner surface of the probe.

15 Preferably the internal diameter of the tubing is between 1.0 mm and 2.0 mm, preferably between 1.2 mm and 1.8 mm and more preferably between 1.4 mm and 1.6 mm, such as about 1.5 mm (1/16 inch). Preferably the length of the tubing is between 0.5 m and 2.5 m, preferably between 1.0 m and 2.0 m and more preferably between 1.3 m and 1.7 m, such as about 1.5 m. This allows for the probe to have  
20 an inner volume enabling the probe to contain a plurality of aspirated volumes of reagent. In this manner the probe may transfer a plurality of reagent volumes from the reagent section to the staining section in a single movement of the probe from the reagent section to the slide section where the plurality of reagent volumes can be dispensed on a plurality of specified microscope slides. This saves considerable  
25 time. This also makes it possible to withdraw a large volume of reagent for staining a multiple of biological samples, e.g. a batch of slides. This results in a fast processing of biological samples in a staining apparatus according to the invention.

30 Preferably the continuous tubing is provided with a spirally wound probe tubing section, and the spirally wound probe tubing section may be a coiled section, wherein the coiled section comprises at least one winding, preferably between 5 and 30 windings, more preferably between 10 and 25 windings, and most preferably between 15 and 22 windings, such as 20 windings. This is advantageous for

accommodation of the long thin tubing. Further the spiral section provides for the flexibility required when the probe is moved up or down.

- 5 In a preferred embodiment the mounting end of the probe member includes a fitting for mounting the device to a probe holder on a probe handling device, such as a robotic head that is part of a computer controlled robotic system in a staining apparatus.

- 10 The invention further provides a reagent container for use in a reagent delivery system according to any of the claims 1 – 6, characterised in that the cross-section of the container is a non-symmetrical polygon. In a preferred embodiment the cross-section of the container is a rectangle with one corner-section replaced by a slanted/oblique fifth side.

- 15 According to the invention a reagent container may have a box-like form, comprising a bottom wall, four side walls and a top wall, and wherein one corner section is replaced by a single slanted/oblique sidewall, ensuring a specified orientation of the container when inserted in a corresponding compartment a reagent container rack, arranged to accommodate a plurality of containers in rows and columns.

- 20 According to the invention there is provided a reagent container assembly for use in a reagent delivery system according to any of the claims 1 – 6, characterised by comprising a covering or shell forming an adapter, which is able to accommodate a reagent container, and further characterised in that the cross-section of the assembly is a non-symmetrical polygon. Preferably the cross-section of the assembly as well as of the reagent container is a rectangle with one corner-section replaced by a slanted/oblique fifth side.

- 25 In a preferred embodiment the reagent container comprises a closure comprising a plurality of sectors, e.g. 4 sectors, such as flaps, which are free to flex upwards or downwards thereby allowing the aspirating end of the reagent dispensing device to penetrate the closure and the closure to regain its closed form after retraction of the probe.

The present invention further presents a method of aspirating and dispensing reagents on a plurality of samples on carriers (tissue slides) in an automated tissue staining apparatus having a slide section, a reagent section and a probe mounted on a robot head of a computer controlled robotic system, characterised by

5 comprising at least one action from the group comprising beginning X-movement of a robot head; moving the robot head an appropriate distance along an X-axis for a probe wash location; ending X-movement of the robot head; beginning Y-movement of a robot head; moving the robot head an appropriate distance along an Y-axis for a probe wash location; ending Y-movement of the robot head; beginning Z-

10 movement of a robot head; lowering a probe tip into a wash area; ending Z-movement of the robot head; switch a valve to activate a probe wash source; open a valve to begin flow of a wash liquid from the probe wash source; wash the probe; close a valve to end flow of a wash liquid from the probe wash source; beginning Z-movement of a robot head; raising the probe tip; ending Z-movement of the robot

15 head; beginning X-movement of a robot head; moving a robot head an appropriate distance along an X-axis for a desired reagent container; ending X-movement of the robot head; beginning Y-movement of a robot head; moving a robot head an appropriate distance along an Y-axis for a desired reagent container; ending Y-movement of the robot head; beginning Z-movement of a robot head; lowering the

20 probe tip over a desired reagent container; ending Z-movement of the robot head; switch a valve to utilize a reagent aspiration pressure source; open a valve to begin access to the reagent aspiration pressure source; aspirate reagent; close a valve to end access to the reagent aspiration pressure source; beginning Z-movement of a robot head; raising the reagent containing probe tip; ending Z-movement of the

25 robot head; beginning X-movement of a robot head; moving a robot head an appropriate distance along an X-axis for a particular slide; ending X-movement of the robot head; beginning Y-movement of a robot head; moving a robot head an appropriate distance along an Y-axis for a particular slide; ending Y-movement of the robot head; beginning Z-movement of a robot head; lowering the reagent

30 containing probe tip over a particular slide; ending Z-movement of the robot head; switch a valve to utilize a reagent emission pressure source; open a valve to begin access to the reagent emission pressure source; emit reagent; close a valve to end access to the reagent emission pressure source; beginning Z-movement of a robot head; raising the empty probe tip; and ending Z-movement of the robot head.

Accordingly any reagent container may be accessed by the probe through a combination of movements of the robotic system – a predetermined volume of reagent or a plurality of predetermined volumes may be aspirated – and later dispensed to one or a plurality of specified slides. The method enables a very efficient and accurate schedule allowing for a high through-put of the apparatus.

5 Preferably according to the method lowering the probe tip over a desired reagent container comprises that the probe tip get in touch with a sealing top closure of the reagent container, and by lowering the probe a further distance the probe penetrates through the sealing top closure of the reagent container; thereby the probe get

10 access to the content, no cap has to be removed – and yet none or very little evaporation.

The present invention further suggests a method of aspirating and dispensing reagents on a plurality of samples on carriers (tissue slides) characterised by

15 aspirating a plurality of predetermined volumes of a predetermined reagent, further characterised by aspirating a predetermined amount of air between each of the predetermined volumes of a reagent, in such a manner that every volume of the plurality of volumes is separated from neighboring volumes by air bubbles. In this manner the plurality of predetermined volumes may be dispensed very accurately

20 on a plurality of slides.

According to this method the probe tubing having aspirated a predefined volume of a first reagent may be removed from the first reagent container, aspirate a predetermined amount of air, forming an air gap or bubble inside the tubing, and

25 then enter into a second reagent container and aspirate the second reagent. The air bubble separates the two reagents and the meniscus of the bubble acts as a wiper within the inner tubing wall to eliminate cross contamination between these two distinct fluids. In similar manner a plurality of different reagents may be aspirated and separated by air during a single period in which the robotic head locates the probe over the reagent section of the stainer Afterwards the computer controlled

30 robotic head can move the probe to the section with the slides, and during the following period dispense one or more reagents on a single or a plurality of slides, possibly requiring different reagents.

- In a preferred embodiment of the invention, the internal diameter of the tubing is 1.5 mm (1/16 inch). The small the internal diameter allows for the air bubble to maintain a stable form as it moves in the tubing. Each single bubble will stay as a single entity and not break up into multiple of bubbles, neither can it collapse with any other bubble. This means that the amount fluid to be dispensed may be controlled accurately, even when a plurality of fluid volumes have been aspirated by the probe. The possibility of aspirating a plurality of separated volumes allows for a fast dispensing of the fluids on one or a plurality of slides in the staining section.

10

#### Brief description of the figures

The invention will now be explained in further detail with reference to the enclosed drawings, showing as non-limiting examples presently preferred embodiments of the invention and wherein

15

Figure 1 is a perspective view of an embodiment of a sample processing apparatus according to the invention.

Figure 2 is a plan view of the apparatus according to the invention.

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Figure 3 shows a schematic view of a robotic head with a probe according to the invention mounted thereon.

Figure 4 shows a first view of an embodiment of a robotic head with a probe according to the invention mounted thereon.

Figure 5 shows a second view perpendicular to the view in Figure 4.

25

Figure 6 is a perspective view of a probe according to an embodiment of the invention;

Figure 7 shows an exploded view of the probe in figure 6,.

Figure 8 shows an embodiment of a washing station.

Figure 9 shows a perspective view of a 50 ml reagent container.

Figure 10 and 11 show side views of the same container.

30

Figure 12 shows a bottom view of the same container.

Figure 13 shows a perspective view of an adapter or covering for accommodation of smaller containers.

Figure 14 a bottom view of the adapter in Figure 13.

- Figure 15 a perspective view of the adapter seen from the top.  
 Figure 16 shows a perspective view of the adapter, seen from the bottom.  
 Figure 17 shows a cross-sectional view along the lines A-A in Figure 14.  
 Figure 18 shows a cross-sectional view along the lines B-B in Figure 14.  
 5 Figure 19 shows a cross-sectional view along the lines C-C in Figure 14.  
 Figure 20 shows a side view of the adapter.  
 Figure 21 shows a perspective view of a 25 ml container.  
 Figure 22, 23 and 25 show side views of the 25 ml container.  
 Figure 24 shows a bottom view of the 25 ml container.  
 10 Figure 26 shows a cross-sectional view of the 25 ml container.  
 Figure 27 shows a perspective view of a 10 ml container.  
 Figure 28 shows a cross-sectional view of the 10 ml container.  
 Figure 29 shows a perspective view of a 5 ml container.  
 Figure 30 shows an upright cross-sectional view of the 5 ml container.  
 15 Figure 31 shows a horizontal cross-sectional view of the 5 ml container.  
 Figure 32 shows a top view of a cap for a container.  
 Figure 33 shows a cross-sectional view of the cap.  
 Figure 34 shows a septum.  
 Figure 35 shows a cross-sectional view of the septum along the line A-A in Figure  
 20 34.

- The embodiments shown in the figures and described in details below is only to be considered as examples of an apparatus in accordance with the present invention and is not limiting the wider scope of the invention as described in the enclosed  
 25 claims. In the below example the sample processing apparatus according to the invention is a staining apparatus.

Example:

- The staining apparatus 1 comprises a frame 4 surrounding at least one reagent station 2 comprising an array of reagent container compartments wherein each compartment a reagent container 3 is placed, and first and second slide sections 5 wherein a number of separate rack assemblies 6 is placed, and where each rack assembly 6 accommodates a number of microscope slides 7 mounted side by side in the rack assembly 6. In the embodiment shown, each rack may hold up to eight  
 30

slides, but the rack may be designed to hold any suitable number of slides. With eight racks arranged side by side, the shown embodiments may hold up to 64 slides 7 each accommodating a biological sample, e.g. a tissue mounted on the upper side of the slide, so that reagent may be applied from above to the sample on each slide.

5

Also the reagent container compartments in reagent section 2 may be arranged as a number of separate container rack accommodating a plurality of reagent container compartments. Preferably the reagent container and the compartment are designed to cooperate in order to avoid a faulty location of a reagent.

- 10 In a preferred embodiment the rack assemblies are arranged as drawers in order to ease the access to slides and reagents.

A robot system arranged to provide for movements in X and Y (as well as Z) directions as indicated by the arrows X and Y is arranged above or within the frame 4 of the staining apparatus. The robot system comprises an arm 20 for moving a fluid dispensing device 10 The robot arm 20 may therefore position the probe 10 above all reagent containers 3 as well as dispense onto all the microscope slides 7, and may further operate the probe 10 to aspirate portions of reagent contained in any of the containers 3, to transfer the portion of reagent and apply it to any of the slides 7 in order to provide a selected staining or treatment of the sample on each slide 7. By use of suitable control means e.g. a computer (not shown) having the appropriate software and input data for the purpose, this staining apparatus 1 is able to automatically stain or treat samples requiring different staining or treatment reagents and processes.

25

As shown in figures 1 and 3 and in more detail in figures 4 and 5, the probe 10 is mounted in a robotic head 22 and may be manipulated by the robot system. The probe 10 may be raised to an upper position (in a Z direction) where it is clear of the containers 3 underneath the probe 10. Further the robot comprises means (which may be of well known kind, such as e.g. a rack and pinion or a hydraulic piston) in the robotic head 22 for lowering the probe 10 in order to insert the probe tip into the content of a selected reagent container or bottle 3 and to aspirate a selected amount of reagent for the selected staining or treatment process. The robotic head 22 may also be provided with further elements such as a CCD camera 25 pointing

30

downwards. The camera may be utilised to acquire (determine) status information of the slides and the reagent containers and other features of the apparatus in the work area, for example reading encrypted information provided on a reagent container to determine the reagent type and the reagent location within the system.

5

The camera may determine status of the tissue sample carriers, for example the location of a particular slide, informational indicia, such as encrypted information, that indicate information or the location of information in a database or the like, about the tissue sample presented on the slide or the processing protocol to be performed. In some embodiments this camera may also be used to locate the sample on the slide, calculate the samples size, and automatically calculate the most efficient volume of reagent required to process the sample. This capability will allow the stainer to automatically adjust the volumes on the fly without user intervention.

15

The staining apparatus 1 of the present embodiment may further comprise a probe washing station 8 and a reagent mixer 9, and the robot system is furthermore arranged to transfer the probe 10 to the washing station 8 as well as to the reagent mixer 9.

20

### **Probe**

The probe 10 is shown in details in figures 6 and 7. The probe comprises a continuous tubing 101 having a spiral section 103 and a probe member 102 having dispensing end also called probe tip 104, and a mounting end having a fitting 105 for mounting on the robot head 22. Preferably the probe member 102 is a rigid tube, which may be made from a metal, such as a 300 series stainless steel, coated with a fluoropolymer, e.g. Teflon <sup>TM</sup>. Preferably also the inner tubing is a fluoropolymer, such as Teflon <sup>TM</sup>. The materials for the probe must be able to withstand the fluids to which it will be exposed during the sample processing. Such fluids may include aqueous, alcoholic, acidic, basic and organic solvent liquids.

30

Preferably the dispensing end 104 is a cone. Preferably the tubing 101 is arranged as an inner lining of the probe member 102 covering the total inner surface of the probe member 102. The other end of tubing 101 ends in a fitting 106 for connection



to a computer controlled pneumatic system, able to provide any desired pressure, enabling the probe to aspirate, with-hold, or dispense predetermined amounts of a fluid. The rigid probe member 102 is mounted with fitting 105 in a holder 205 on the robotic head 22.

5

Preferably the holder 205 is mounted in a rack and pinion drive and may be moved in a vertical direction raising or lowering the probe relative to the underlying samples.

- 10 The spirally wound section 103 comprises at least one winding and preferably a plurality of windings. It is advantageous in that it may flex as the probe 10 is moved up or down or in any other direction by the robotic head 22. Additionally, this section of tubing in the spirally wound section 103 may provide for a considerably increased internal volume in the tube, so that the probe may hold a relatively large fluid
- 15 content.

Example: In a preferred embodiment the inner diameter of the tubing 101 is about 1.5 mm. In one embodiment the probe shall be able to aspirate a volume of about 2.5 ml. Accordingly the length of the tubing has to be about 1.5 m. Such length may

20 be accommodated/achieved by including a coil section having about 20 windings and a diameter of about 20 mm providing for about 1260 mm. Adding thereto the length of the rigid probe member and the tubing section from the coil to the fitting 106 a total of 1.5 m may be obtained. Obviously the tube may be designed to accommodate other fluid volumes. The inner diameter of the tubing is determined

25 such that the viscosity of the fluid will secure the fluid in the probe during the movement of the probe from reagent container to a mixer and/or a slide.

- Preferably, the robotic head is adapted to lower the probe 10 when it is aligned on top of a selected reagent container. In a preferred embodiment a reagent container
- 30 is covered by a cover through which, the probe tip 104 may penetrate forced by the robotic head. It is advantageous that the probe 10 is capable of automatically gaining entry into the container, as this allows for a "closed" container design, i.e. a reagent container that constantly through all lifetime of use is provided with a protecting cover or septum.

When having pierced the cover or septum, a predetermined amount of the fluid in the container is aspirated into the tubing, and the probe is raised. After having aspirated a predetermined volume of fluid into the probe, it may be advantageous to  
5 aspirate some air in order to reduce risk of losing a drop of reagent during the robotic transfer of the probe including the fluid to the staining section accommodating the slide for which the reagent is intended. The robotic head moves the probe until it is located right over the slide, and the probe may be lowered until it is located a predetermined distance above the slide. Then a valve opens for a short  
10 moment to the pneumatic device providing a short interval of a pressure dispensing the predetermined volume of reagent to the tissue on the slide.

Alternatively, with the probe raised above a reagent container an air gap may be created by aspirating air and the probe may be lowered into the reagent container  
15 again aspirating a second volume of the same reagent, raised again repeating the aspiration of air and reagent a plurality of times (typically 5 – 10 times). After having aspirated a plurality of predetermined volumes of reagent for a plurality of predetermined slides the robotic head moves the probe including fluid and air to the staining section accommodating the slides for which the reagent is intended. This  
20 procedure may be very timesaving as the probe is only moved once from the reagent section towards the slide section. It is useful if the same reagent has to be dispensed on a plurality of slides.

In a further alternative procedure and after having aspirated a first fluid and a first air  
25 gap into the probe, a second fluid may be aspirated into the probe tubing from another reagent container and a second air gap and so on until reagents for a plurality of slides has been aspirated.

The pneumatic system may control the pressure in the probe tube, providing e.g. a  
30 vacuum or a pressure below or above the atmospheric pressure according to control signals, preferably generated by a computer, and preferably according to schedules for the treatment of the slides inserted into the stainer. By having "active" vacuum in the tubing of the probe according to the invention, the design of the reagent

containers is not critical for ensuring that a predetermined amount of reagent is transferred from the container.

- With the probe according to the invention it is possible to provide both precision and accuracy of the aspirated volumes of reagents. This is very important as the staining  
 5 result may be deteriorated if the applied volumes differ from the recommended sizes, and this could later cause difficulties when analysing the stained sample in a microscope and might give reason to a faulty diagnosis.

Example:

- 10 Specification for Precision:  
 CV< 10% at 100  $\mu$ l and increments of 100 $\mu$ l to 600 $\mu$ l dispense volumes.  
 20% CV at 20  $\mu$ l, 40  $\mu$ l, and 50  $\mu$ l.  
 Specification for Accuracy:  
 95% at 100  $\mu$ l and increments of 100  $\mu$ l to 600  $\mu$ l dispense volumes.  
 15 20% CV at 20  $\mu$ l, 40  $\mu$ l and 50  $\mu$ l.

Whenever needed – and typically when a different reagent is to be aspirated and dispensed - the robot system may move the probe to a washing station 8, able to clean the probe 10, removing all traces from the preceding reagent.

20

- In a preferred embodiment the washing station 8 comprises deep receptacle 81 able to accommodate a length of the rigid probe member 102 at least corresponding the length, which may have been dipped into the reagent. Through valves (not shown) the tubing end with fitting 106 may be connected to a source of at least one wash  
 25 solution or cleaning fluid, which will pass through the tubing and finally be ejected from the probe tip into the washing receptacle 81. Further the wash solution or cleaning fluid passes on along the outer surface of the probe 102 and exit the receptacle 81 through an outlet 82 to waste arranged a distance above the bottom and preferably close to the top of the receptacle 81. The receptacle 81 may be  
 30 emptied by opening a normally-closed bottom valve 83.

In order to dry the probe after the wash, thereby removing any traces of the cleaning fluids, a stream of air may be directed through the probe by connecting the tubing end with the fitting 106 through a valve to an air source.

**Reagent containers:**

In a preferred embodiment the reagent containers or bottles are designed to fit into the reagent section of the sample processing apparatus, and to cooperate with the design of the probe.

- 5
- Preferably the reagent section comprises a plurality of receptacles able to receive a plurality of reagent containers. Preferably a cross section of these receptacles corresponds to a cross-section of the reagent container. Further preferably the cross-section is a non-symmetrical polygon. In a presently preferred embodiment
- 10
 

shown in several of the Figures 9-31 the cross-section is a pentagon, and more specifically a pentagon having two sides, and 3 angles in common with a rectangle. In other words the preferred cross-section is a rectangle with one corner-section replaced by a slanted/oblique fifth side.
- 15
 

The advantage is that the containers can only be arranged in the receptacles with a specific orientation. Also any other container of different design cannot fit into the receptacle. This may contribute to avoid faulty supply of reagents. You may say the containers are keyed.
- 20
 

This is very important as the top of the container (shown in Figures 9, 21, 27, 29) in a preferred embodiment comprises two features: 1) a neck 137 with a cover providing access to the fluid content, and 2) an identification 138 relating to the content of the container, preferably including information specific to the content, such as e.g. name of chemical substance, date of delivery, date of expiration, and
- 25
 

any other relevant information. Alternatively the identification could be a coded number providing access through a computer to an address comprising such information. It is essential for the automated robotic control of the probe movements that the containers are located precisely in the predetermined positions in the receptacles in the reagent section, so the probe when lowered will hit the cover of
- 30
 

the container. Also—at the same time - the camera (or another sensor device) may read the identification and control that the correct reagent will be aspirated.

In a preferred embodiment the computer system controlling the operation of the robotic system is programmed to start a new sample processing by performing a search of all reagents, identifying the location of the various reagents, preferably using the probe to measure the level of all reagents. In a further preferred embodiment the computer system is programmed to alert the user if a reagent level is too low to accomplish the staining task for which it is set up. To accomplish this automated operation it is essential that the reagent containers remain fixedly located in the identified positions. Accordingly the design of the reagent containers must cooperate tightly with the design of the receptacles in the rack assemblies wherein they are located.

In one embodiment, illustrated in figures 9-12 the container is a 50 ml container having a cross-section that is a rectangle with one corner-section replaced by a slanted/oblique fifth side. The container or bottle comprises a bottom 130, five upright sides 131, 132, 133, 134,135 and a top 136 with a neck 137. In a preferred embodiment the top as shown in details in Figure 10 has a label 138 that identifies the content of the container.

In view of the fact that some reagents are used in various volumes or even seldom, and still others may have a short shelf-life, having to be replaced often, there is a need for providing the reagents in containers having different volumes. In order to be able to arrange a plurality of containers having different volumes in the same reagent station with a plurality of identical receptacles it is suggested to provide an assembly comprising a tube-like covering or shell called "an adapter" and an internal bottle which may be provided in different sizes, having internal volumes of e.g. 1 ml, 2 ml, 5 ml, 10 ml, 15 ml, 20 ml, 25 ml or similar volumes. Generally the typical reagent volume for an apparatus according to the present invention will be between about 1 ml and 25 ml.

#### 30 Covering-adapter:

In a preferred embodiment the covering is a tube-like element 200 having the same outer cylindrical surface as the 50 ml container, i.e. the cross-section is a rectangle with one corner-section replaced by a slanted/oblique fifth side.

- In order to allow for the computer-controlled automated aspiration of reagents it is essential that the internal bottles are arranged in a fixed manner inside the tube-like covering enabling the probe to penetrate in a well-defined manner into the fluid content of the bottle. This is achieved by providing the covering and the inner bottles with corresponding projections and indentations respectively and/or vice versa, ensuring a well-defined position of the inner bottle inside the covering. The projections shall ensure a correct orientation in all directions. It shall be impossible to insert the inner bottle in any other way than the intended.
- 10 In a preferred embodiment this is achieved through the combination of projections and indentations shown in the Figures 14-19 and 21-30.

- Projections 221, 222 in the narrow sides 231, 233 of the adapter 200 will cooperate with the bottom of an inner bottle such as a 10 ml bottle 250 shown in Figures 27-28. Further projections 223, 224, in the same sides cooperate with indentations 251, 252 in the bottle. In this manner the bottle will remain in the fixed position in the adapter, even when exposed to the pressure from a probe being inserted through a top cap. A 25 ml bottle shown in Figure 21 has further indentations 261, 262 allowing this bottle to pass by the projections 221, 222.

- 20 In a preferred embodiment the inner bottle 250 has a neck 255 with an external thread 256 and a corresponding cap 320 shown in Figures 32-23 with an internal thread 322, providing a closure for the bottle 250. The cap 320 may comprise a circular opening through which the probe may aspirate the fluid content in the bottle.
- 25 In this manner no operator has to unscrew cap in order to provide access to the content. The probe may simply reach the fluid content when the probe is lowered by the robotic system until the probe gets in touch with the fluid. Preferably the probe is in electrical connection with electronic circuits enabling a determination of the fluid level in the container. Alternatively and in some embodiments a second database method of reagent volume tracking may be used instead of or in conjunction with previously detailed electronic method. The database method employs the use of a database to track the usage of a reagent removed by the probe from a specific container and calculates the remaining available volume.
- 30

However, in order to protect the reagent fluids from contamination as well as evaporation it is highly recommendable to provide tight closures for the bottles. To this end the circular opening in the cap 320 has a skirt 324 with a peripheral edge 326 including a peripheral outwardly projecting rim or lip 328 and a  
 5 peripheral/surrounding indentation or groove 329 able to cooperate with and fixate a corresponding septum 340 in a flexible material such as polypropylene, 35A. The corresponding septum 340 has an upward skirt 344 with an inwardly projecting rim or lip 346 and groove/indentation 348, able to cooperate with the indentation 329 and rim/lip 328 inside the cap 320. When the cap is secured to the bottleneck 255  
 10 the upper end of the neck will support and force the lip 346 to stay locked in the groove 329

Preferably the septum 340 comprises a plurality of sectors or flaps 351, 352, 353, such as 2, 3 or 4 sectors, which are free to flex upwards or downwards thereby  
 15 allowing a probe to penetrate the septum. After aspiration of the predetermined amount of fluid the probe is raised again, thereby being retracted from the reagent bottle. During retraction of the probe the flaps will wipe off the reagent from the outer surface of the probe. After retraction of the probe the flaps return to their original position forming an almost tight closure inside the cap on top of the bottle. This  
 20 septum has several advantages: Evaporation of reagent is reduced, and the wiping action of the flaps saves reagent from being carried away on the outer surface of the probe when the probe is raised for movement to the slide section.

#### Preferred modes of operation:

25 An operator enters relevant input data - relating to a requested processing of a number of slides, which are to be processed, - on a computer connected to the control system controlling one or more sample processing apparatus, such as stainers. When a stainer is vacant or a requested number of slide positions in a rack in a drawer of a stainer are vacant the slides are loaded into the vacant position.

30 Having the appropriate input data, the control means of the apparatus operates the robot arm to commence a processing of the slides. When a reagent is needed for a staining or treatment the robot moves the probe to a first reagent container 3, into which the probe tip 12 is inserted into the reagent, and reagent is aspirated into the

probe 10 in an amount corresponding to the number of samples to be stained or treated, in accordance with the input data provided to the control means.

5 The probe 10 is subsequently, in a first operating mode moved by the robot arm towards the slide rack system 5 in which the slides 7 are mounted. The slides 7 are situated with the surface horizontally oriented and the probe 10 releases the required amount of reagent on the appropriate slides in accordance with the input data. Alternatively, the probe 10 in a second operating mode may be moved by the robot arm towards the reagent mixer 9 where it releases the reagent into the cup 13  
10 of the reagent mixer 9, and is subsequently moved to the probe washing station 8, where the probe 10 is washed and dried. The robot arm moves the newly cleaned probe 10 to a second selected reagent vial 3 for collecting a selected amount of reagent from the second vial 3, and the probe 10 is thereafter by means of the robot arm moved to the reagent mixer 9, where the reagent in the probe 10 is dispensed  
15 into the cup 13 of the mixer containing the first selected reagent. The second operating mode can according to the invention be commenced several times if more than two reagents are to be mixed for a specific staining or treatment process. After thorough mixing the required amount of mixed reagents are dispensed on the appropriate slides in accordance with the input data.

20 Subsequently the robot arm with probe 10 is directed to the washing station 8, and the probe 10 is washed and dried, where after the process in accordance with the first or the second operating mode may be repeated or continued with new reagents or reagent mixtures according to processing steps defined in a protocol for the  
25 treatment of the slides.

According to a preferred method the probe tubing having aspirated a predefined volume of a first reagent may be removed from the first reagent container, aspirate a predetermined amount of air, forming an air gap or bubble inside the tubing, and  
30 then enter into a second reagent container and aspirate the second reagent. The air bubble separates the two reagents and the meniscus of the bubble acts as a wiper within the inner tubing wall to eliminate cross contamination between these two distinct fluids. In similar manner a plurality of different reagents may be aspirated and separated by air during a single period in which the robotic head locates the



- probe over the reagent section of the stainer. Afterwards the computer controlled robotic head can move the probe to the section with the slides, and during the following period dispense one or more reagents on a single or a plurality of slides, possibly requiring different reagents. Aspirating a plurality of volumes for a plurality of microscope slides is very time-saving, supporting a high through-put of the apparatus, as the probe only moves once from reagent section to the staining section with the slides, yet dispensing a plurality of reagent volumes on a plurality of slides.
- 10 Returning to the aspect of monitoring or capturing information, an embodiment of the system may be designed to monitor replenishable supply information, such as the status of buffers, reagents, stains or the like. By monitoring for a potential need for replenishable supplies the system may remove at least one possibility for human error. Significantly, the system may also act to automatically notify any number of
- 15 people relative to the information monitored. With respect to replenishable supply information, the system may notify a user, an operator, an administrator, or even a supplier of an actual, potential, or impending need to replenish supplies. As such the system may be considered as including an automatic notice element, or the like.
- 20 The invention is described above with reference to a preferred embodiment. However, it is realised that variants may be provided without departing from the scope of the invention as defined in the accompanying claims.

- List of components:
- staining apparatus 1
  - reagent station 2, section
  - 5 reagent container – (bottle) - vial 3
    - frame 4
    - first and second slide sections 5, staining section
    - rack assemblies 6, rack system
  - 10 microscope slides 7, carrier elements (for biological samples)
    - probe washing station 8
    - receptacle 81 in 8
    - outlet 82
  - 15 bottom valve 83
    - reagent mixer 9,
    - fluid dispensing device 10; probe 10
    - reagent dispensing device 10 - probe
    - robotic motion system
  - 20 robot arm 20 – robotic arm –
    - robotic head 22;
    - CCD camera 25
    - flexible tube,
    - continuous probe tubing element 101
  - 25 probe member 102
    - spirally wound section 103 coil; winding;
    - nozzle end, aspirating and dispensing end 104
    - probe mounting end 105
    - connection fitting 106 -
  - 30 holding means, holder 205
    - pneumatic pressure regulation device (not shown)
    - 50 ml container bottle 125
    - identification 156
  - 35 bottom 130, sides 131,132, 133, 134, 135, top 136, neck 137, label 138.
    - Covering hylster - shell 200
    - sides 231,232, 233, 234, 235,
    - projections 221,222, 223, 224
  - 40 25 ml container bottle 250– container body
    - Indentations 251, 252
    - neck - upper opening 255
    - external thread 256
    - cap 320 – internal thread 322
  - 45 skirt 324, edge 326, rim/lip 328,
    - groove / indentation 329
    - septum 340, upward skirt 344,
    - projection/ rim/lip 346
    - indentation/groove 348
  - 50 flaps 351-353

## PATENT CLAIMS:

1. A reagent delivery system in an apparatus for processing biological samples arranged on carrier elements, the apparatus comprising a stationary reagent  
5 section having one or more reagent containers and a stationary staining section in which at least one carrier element is arranged; and wherein the reagent delivery system comprises a probe for aspirating a portion of reagent from a reagent container in order to dispense a predetermined amount on a predetermined carrier element,  
10 a probe handling device for handling the probe; wherein the probe comprises a continuous probe tubing (101) extending through a rigid probe member (102) and providing fluid communication from a dispensing end (104) of said probe member to a pneumatic pressure regulation device and wherein the rigid probe member is adapted for cooperation with the  
15 closure of the reagent container.
2. A reagent delivery system according to claim 1, wherein the rigid probe member is arranged to cooperate with at least one reagent container in such manner that the probe may penetrate an opening covered by cap comprising a septum,  
20 aspirate reagent, and withdraw from the container, and wherein the septum is adapted to regenerate as an almost tight closure of the reagent container, i.e. become substantially closed again.
3. A reagent delivery system according to claim 2, wherein the septum comprises a  
25 plurality of sectors, e.g. 4 sectors, such as flaps, which are free to flex upwards or downwards thereby allowing the aspirating end of the probe to penetrate the closure and the closure to almost regain its closed form after retraction of the probe.
- 30 4. A reagent delivery system according to claim 2, wherein the septum comprises a plurality of sectors, e.g. 4 sectors, such as flaps, which originally are connected by lines of weakness, and wherein the lines of weakness will break the first time a probe is inserted into the reagent container, and afterwards are free to flex upwards or downwards thereby allowing the aspirating end of the probe to

penetrate the closure and the closure to almost regain its closed form after retraction of the probe.

- 5 5. A reagent delivery system according to claim 1 or 2, wherein the dispensing end of the probe is a cone in order to facilitate the penetration through the septum in the closure of the reagent container.
- 10 6. A reagent delivery system according to claim 1, characterised in that a reagent container is provided with an identification, and that the probe handling device comprises a robotic device also comprising a sensor element able to acquire information from the identification on the reagent container, and wherein the robotic device is connected to a computer receiving the acquired information.
- 15 7. A staining apparatus for automated processing of biological samples arranged on carrier elements, comprising  
a reagent section comprising one or more reagent containers;  
a staining section in which at least one carrier element is arranged;  
a reagent dispensing device for dispensing a portion of reagent onto a predetermined carrier element,  
20 a handling device for handling said reagent dispensing device;  
wherein the reagent dispensing device comprises a continuous probe tubing extending through a rigid probe member and providing fluid communication from a dispensing end of said probe member to a pneumatic pressure regulation device.
- 25 8. A staining apparatus according to claim 7, wherein the pneumatic pressure regulation device include a vacuum source with which the tubing may communicate via a valve device.
- 30 9. A staining apparatus according to claim 8, wherein said valve device are operable to provide a predetermined pressure in the tubing for aspirating or dispensing a predetermined amount of reagent in the dispensing end of the tubing.

10. A staining apparatus according to any of the claims 7-9, wherein the handling device includes  
a holder for holding the probe member; and  
5 a robotic motion system for moving the reagent dispensing device between predetermined locations relative to the carrier element and the reagent containers.
- 10 11. A staining apparatus according to any of the claims 7 to 10, wherein the internal diameter of the tubing is between 1.0 mm and 2.0 mm, preferably between 1.2 mm and 1.8 mm and more preferably between 1.4 mm and 1.6 mm, such as about 1.5 mm (1/16 inch)
- 15 12. A staining apparatus according to any of the claims 7 to 11, wherein the length of the tubing is between 0.5 m and 2.5 m, preferably between 1.0 m and 2.0 m and more preferably between 1.3 m and 1.7 m, such as about 1.5 m.
- 20 13. A staining apparatus according to any of claims 7 to 12, wherein the continuous tubing is provided with a spirally wound probe tubing section.
14. A staining apparatus according to claim 13, wherein the spirally wound probe tubing section is a coiled section.
- 25 15. A staining apparatus according to claim 14, wherein the coiled section comprises at least one winding, and preferably between 5 and 30 windings, more preferably between 10 and 25 windings, and most preferably between 15 and 22 windings, such as 20 windings.
- 30 16. A staining apparatus according to any of claims 7 to 15, further including a washing station for cleaning the reagent-dispensing device.
17. A staining apparatus according to claim 8 and 16, wherein said valve device are adapted to provide a connection to a fluid source providing a wash solution or cleaning fluid for washing and or rinsing the probe tubing.

18. A staining apparatus according to claims 14 and 16, wherein the washing station comprises a receptacle (wash sump) able to accommodate a substantial portion of the dispensing end of the probe, and an outlet to waste.
- 5
19. A staining apparatus according to claim 18 wherein the outlet to the waste is located a distance above the bottom of the receptacle so that the wash fluid ejected from the dispensing end of the probe will wash the outer surface of the dispensing end of the probe before the wash fluid is drained to waste.
- 10
20. A staining apparatus according to any of the claims 17 to 19, wherein said washing fluid are selectable from a plurality of fluids according to the tube cleaning requirements.
- 15
21. A staining apparatus according to any of the claims 7 to 20, wherein the reagent section comprises a reagent rack providing a plurality of compartments for a plurality of reagent containers or container assemblies and wherein the cross-section of a compartment cooperates with the cross-section of the container or container assembly.
- 20
22. A staining apparatus according to claim 21, wherein the cross-section is an unsymmetrical polygon, such as a rectangle with one corner-section replaced by a slanted/oblique fifth side.
- 25
23. A staining apparatus according to claim 22, wherein a top wall of a reagent container is provided with a label comprising information identifying e.g. type of reagent, container volume size, date of delivery, date of end of use, and wherein the robot head further comprises an optical sensor, able to provide the information on the label to a computer system.
- 30
24. A staining apparatus according to claim 22, wherein an electrically conducting member of the reagent dispensing device is connected to an electronic circuit adapted for capacitive level sensing. (able to detect the reagent level by sensing

an electrical capacity, and adapted to forward information about the detected level to the computer system). – adapted for capacitive level sensing.!!

25. A staining apparatus according to claim 22, wherein the computer system will  
5 issue an order for a new delivery of the reagent if the level is below a predetermined limit.
26. A staining apparatus according to claim 22, wherein the computer system is  
connected to a plurality of staining apparatus, and further  
10 uses the reagent dispensing device to detect the level of reagent fluid in each reagent container  
is arranged to let the robotic system with the level sensor and the optical sensor  
update information about the available amount of reagent in the reagent  
containers in the plurality of staining apparatus before starting a staining  
15 procedure and further  
wherein the computer system is arranged to recommend to an operator that a  
tissue slide requiring a specific reagent, be processed in a staining apparatus  
having a reagent container comprising the necessary volume of such specific  
reagent.  
20
27. A reagent dispensing device for use in a staining apparatus for processing of  
biological samples arranged on carrier elements, said device comprising  
a probe member having  
an aspirating and dispensing end, through which reagent may be aspirated and  
25 dispensed, and a mounting end; and wherein  
a continuous probe tubing is provided inside the probe member, said tubing  
extending from the aspirating and dispensing end through the entire probe  
member to pneumatic pressure regulation device.
- 30 28. A reagent dispensing device according to claim 27, wherein the internal  
diameter of the tubing is between 1.0 mm and 2.0 mm, preferably between 1.2  
mm and 1.8 mm and more preferably between 1.4 mm and 1.6 mm, such as  
about 1.5 mm (1/16 inch).

29. A reagent dispensing device according to claim 27 or 28, wherein the length of the tubing is between 0.5 m and 2.5 m, preferably between 1.0 m and 2.0 m and more preferably between 1.3 m and 1.7 m, such as about 1.5 m.
- 5 30. A reagent dispensing device according to any of the claims 27 to 29, wherein the continuous tubing is provided with a spirally wound probe tubing section.
31. A reagent dispensing device according to claim 30, wherein the spirally wound probe tubing section is a coiled section.
- 10 32. A reagent dispensing device according to claim 31, wherein the coiled section comprises at least one winding, preferably between 5 and 30 windings, more preferably between 10 and 25 windings, and most preferably between 15 and 22 windings, such as 20 windings.
- 15 33. A reagent dispensing device according to any of claims 27 to 32, wherein the mounting end of the probe member includes a fitting for mounting the device to a probe holder on a probe handling device, such as a robotic head that is part of a computer controlled robotic system in a staining apparatus.
- 20 34. A reagent container for use in a reagent delivery system according to any of the claims 1 – 6, characterised in that the cross-section of the container is a non-symmetrical polygon.
- 25 35. A reagent container according to claim 34, wherein the cross-section of the container is a rectangle with one corner-section replaced by a slanted/oblique fifth side.
- 30 36. A reagent container having a box-like form, comprising a bottom wall, four side walls and a top wall, and wherein on corner section is replace by a single slanted/oblique sidewall, ensuring a specified orientation of the container when inserted in a corresponding compartment a reagent container rack, arranged to accommodate a plurality of containers in rows and columns.



37. A reagent container assembly for use in a reagent delivery system according to any of the claims 1 – 6, characterised by comprising a covering or shell forming an adapter which is able to accommodate a reagent container and further characterised in that the cross-section of the assembly is a non-symmetrical polygon.
38. A reagent container assembly according to claim 37, wherein the cross-section of the assembly as well as of the reagent container is a rectangle with one corner-section replaced by a slanted/oblique fifth side.
39. A reagent container assembly according to claim 37, wherein the reagent container comprises a closure comprising a plurality of sectors, e.g. 4 sectors, such as flaps, which are free to flex upwards or downwards thereby allowing the aspirating end of the reagent dispensing device to penetrate the closure and the closure to regain its closed form after retraction of the probe.
40. A method of aspirating and dispensing reagents on a plurality of samples on carriers (tissue slides) in an automated tissue staining apparatus having a slide section, a reagent section and a probe mounted on a robot head of a computer controlled robotic system, characterised by comprising at least one action from the group comprising
- beginning X-movement of a robot head;
  - moving the robot head an appropriate distance along an X-axis for a probe wash location;
  - ending X-movement of the robot head;
  - beginning Y-movement of a robot head;
  - moving the robot head an appropriate distance along an Y-axis for a probe wash location;
  - ending Y-movement of the robot head;
  - beginning Z-movement of a robot head;
  - lowering a probe tip into a wash area;
  - ending Z-movement of the robot head;
  - switch a valve to activate a probe wash source;
  - open a valve to begin flow of a wash liquid from the probe wash source;

- wash the probe;
- close a valve to end flow of a wash liquid from the probe wash source;
- beginning Z-movement of a robot head;
- raising the probe tip;
- 5     ending Z-movement of the robot head;
- beginning X-movement of a robot head;
- moving a robot head an appropriate distance along an X-axis for a desired reagent container;
- ending X-movement of the robot head;
- 10    beginning Y-movement of a robot head;
- moving a robot head an appropriate distance along an Y-axis for a desired reagent container;
- ending Y-movement of the robot head;
- beginning Z-movement of a robot head;
- 15    lowering the probe tip over a desired reagent container;
- ending Z-movement of the robot head;
- switch a valve to utilize a reagent aspiration pressure source;
- open a valve to begin access to the reagent aspiration pressure source;
- aspirate reagent;
- 20    close a valve to end access to the reagent aspiration pressure source;
- beginning Z-movement of a robot head;
- raising the reagent containing probe tip;
- ending Z-movement of the robot head;
- beginning X-movement of a robot head;
- 25    moving a robot head an appropriate distance along an X-axis for a particular slide;
- ending X-movement of the robot head;
- beginning Y-movement of a robot head;
- moving a robot head an appropriate distance along an Y-axis for a particular slide;
- 30    ending Y-movement of the robot head;
- beginning Z-movement of a robot head;
- lowering the reagent containing probe tip over a particular slide;
- ending Z-movement of the robot head;

- switch a valve to utilize a reagent emission pressure source;  
open a valve to begin access to the reagent emission pressure source;  
emit reagent;  
close a valve to end access to the reagent emission pressure source;  
5     beginning Z-movement of a robot head;  
       raising the empty probe tip; and  
       ending Z-movement of the robot head.
41. A method according to claim 40 wherein lowering the probe tip over a desired  
10     reagent container comprises that the probe tip get in touch with a sealing top  
       closure of the reagent container, and by lowering the probe a further distance  
       the probe penetrates through the sealing top closure of the reagent container;
42. A method of aspirating and dispensing reagents on a plurality of samples on  
15     carriers (tissue slides) characterised by aspirating a plurality of predetermined  
       volumes of a predetermined reagent, further characterised by aspirating a  
       predetermined amount of air between each of the predetermined volumes of a  
       reagent, in such a manner that every volume of the plurality of volumes is  
       separated from neighbouring volumes by air bubbles.
- 20

## ABSTRACT:

- The invention concerns reagent delivery system for an apparatus for processing of biological samples arranged on microscope slides, comprising a reagent section
- 5 having one or more reagent containers; a slide section in which at least one microscope slide is arranged; a probe for dispensing a portion of reagent onto a predetermined microscope slide, and means for handling the probe. The probe comprises a continuous probe tubing element extending through a rigid probe member and connecting the probe tip to a pneumatic pressure regulation device.
- 10 The reagent containers are adapted for cooperation with the probe tip.

In this manner a high through-put and a very low carry over of fluid residues is achieved since there is no assembled parts making up the inside volume of the probe in which the fluid may be retained.

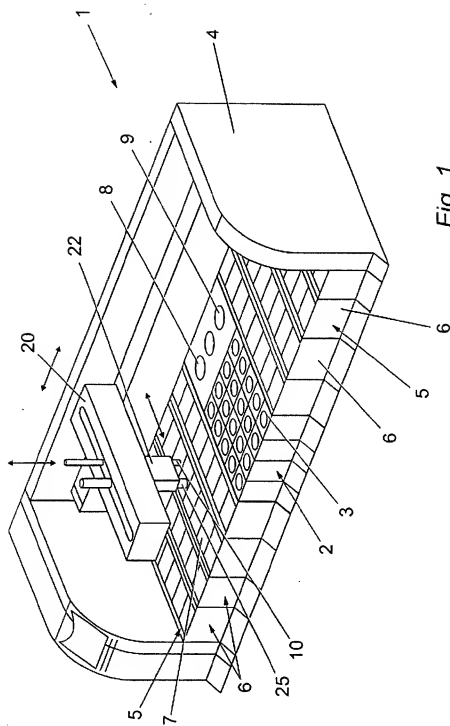
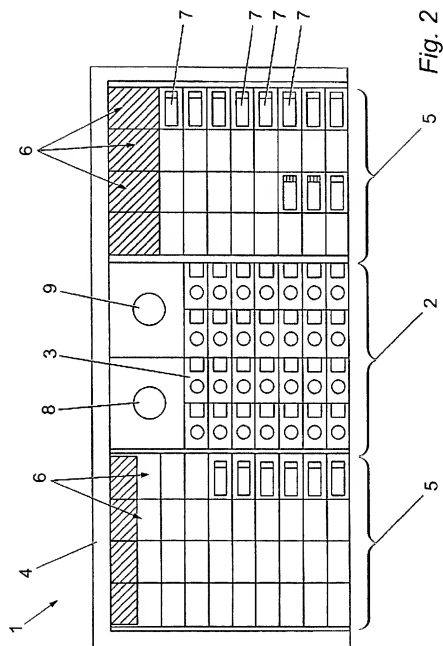


Fig. 1



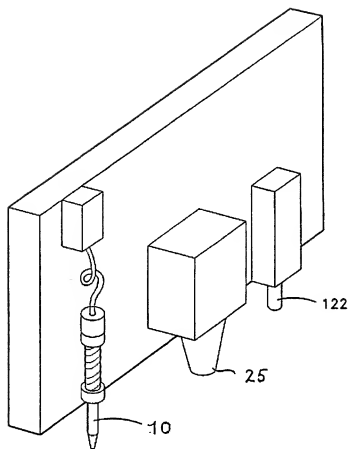


Fig. 3

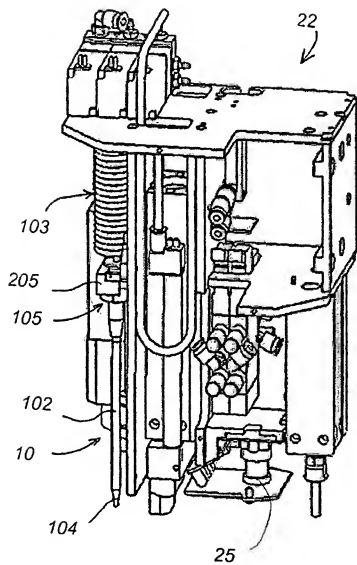


Fig. 4



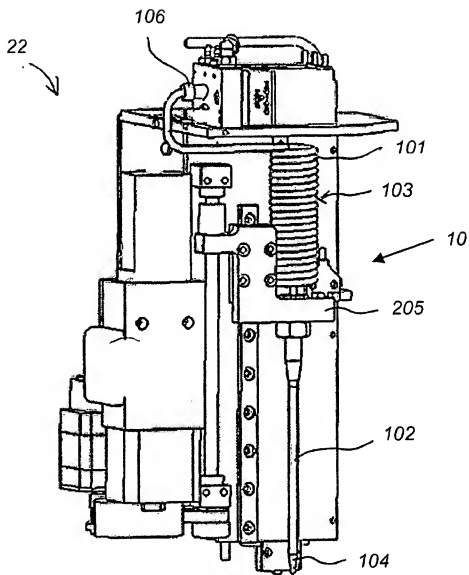


Fig. 5

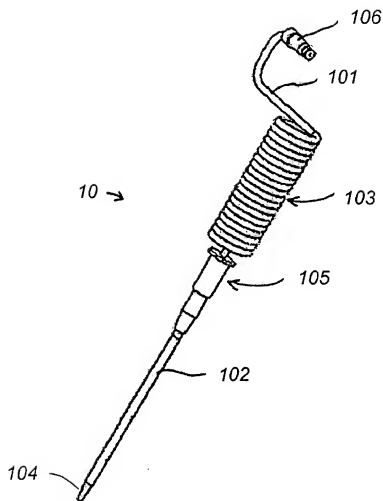


Fig. 6

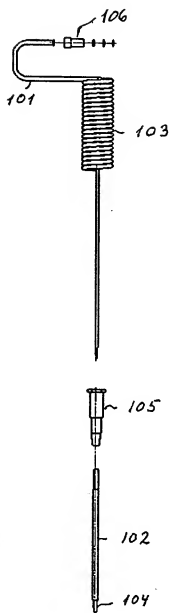


Fig. 7

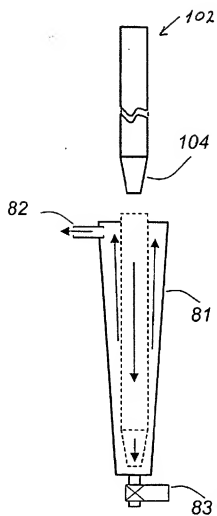


Fig. 8

Fig. 9

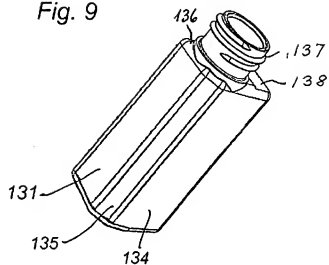


Fig. 10



Fig. 11

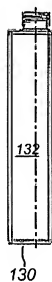


Fig. 12

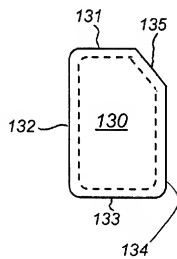


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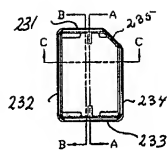
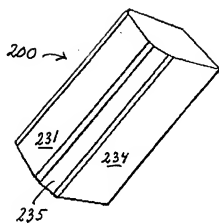


Fig 14

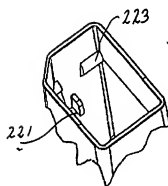


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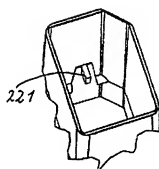


Fig 16

Fig 17

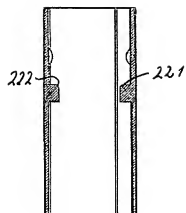


Fig 18

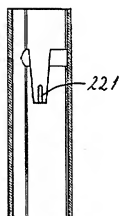
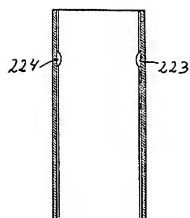


Fig 19

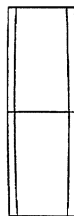


Fig 20

Fig.21

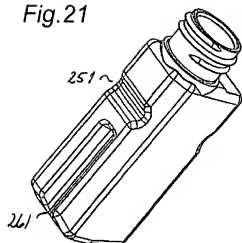


Fig.22

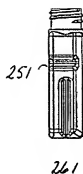


Fig.24

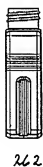


Fig.23

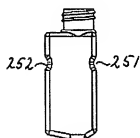


Fig.25

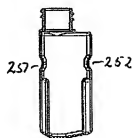


Fig.26



Fig. 27

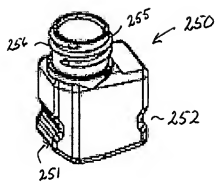


Fig. 28

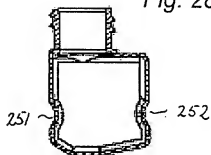


Fig. 29

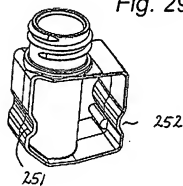


Fig. 30

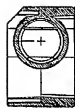
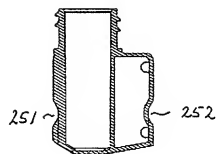


Fig. 31

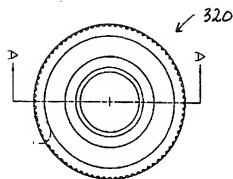


Fig. 32

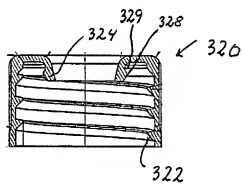
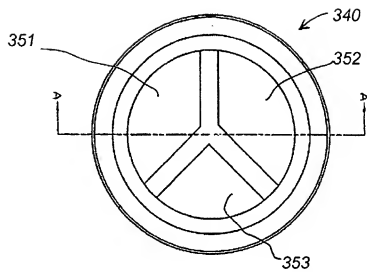
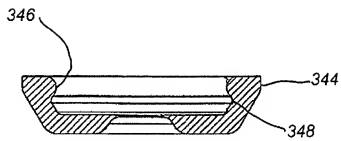


Fig. 33

*Fig. 34**Fig. 35*

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UNITED STATES PATENT AND  
TRADEMARK OFFICE

In Re the Provisional Application of: John Favuzzi, Kristopher Buchanan, Merritt M. Martin, Jr.,  
Loren Bland, Jonathan Sweda, Robert Lathrop, John Van  
Bosch

Serial Number:

Filed:

For: A Reagent Delivery System and A Staining Apparatus For Processing  
Biological Samples and A Reagent Dispensing Device and A Reagent  
Container for Use in Such Delivery Systems

Assignee: DakoCytomation Denmark A/S

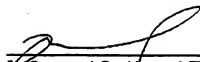
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POWER OF ATTORNEY

I, Jes Ostergaard, President and CEO, DakoCytomation Denmark A/S, hereby appoint Santangelo Law Offices, P.C., whose mailing address is 125 South Howes, Third Floor, Fort Collins, Colorado 80521, including Luke Santangelo, whose registration number before the United States Patent and Trademark Office is 31,997, Nicole A. Ressue, whose registration number before the United States Patent and Trademark Office is 48,665, Alfred K. Wiedmann Jr., whose registration number before the United States Patent and Trademark Office is 48,033, and Misha Gregory Macaw, whose registration number before the United States Patent and Trademark Office is 55,417 as DakoCytomation Denmark A/S attorneys to prosecute this application entitled "A Reagent Delivery System and A Staining Apparatus For Processing Biological Samples and A Reagent Dispensing Device and A Reagent Container for Use in Such Delivery Systems" and to transact all business in the Patent Office connected therewith. The undersigned grants the firm of Santangelo Law Offices, P.C., the power to insert on any document filed in this matter any further identification which may be necessary or desirable in order to indicate filing information or to comply with the rules of the United States Patent Office or any foreign patent office for recordation of this document, including, but not limited to, inserting the application number, the execution date, mailing information, or the filing date of the above-identified United States Patent Application based upon the Invention. The undersigned acknowledges that the attorneys appointed are attorneys for the assignee, DakoCytomation Denmark A/S, only.

Dated this 1 day of March, 2004.

By:

  
\_\_\_\_\_  
Jes Ostergaard, President and CEO  
DakoCytomation Denmark A/S

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UNITED STATES PATENT AND  
TRADEMARK OFFICE

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In Re the Provisional Application of: John Favuzzi, Kristopher Buchanan, Merritt M. Martin, Jr.,  
Loren Bland, Jonathan Sweda, Robert Lathrop, John Van  
Bosch

Serial Number:

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For: A Reagent Delivery System and A Staining Apparatus For Processing  
Biological Samples and A Reagent Dispensing Device and A Reagent  
Container for Use in Such Delivery Systems

Assignee: DakoCytomation Denmark A/S

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APPLICATION DATA SHEET

**Application Information**

Application Type::	Provisional
Subject Matter::	Utility
CD-ROM or CD-R::	None
Title::	A Reagent Delivery System and A Staining Apparatus For Processing Biological Samples and A Reagent Dispensing Device and A Reagent Container for Use in Such Delivery Systems
Attorney Docket::	DakoCytoProbe-P118
Request for Early Publication?::	No
Request for Nonpublication?::	No
Suggested Drawing Figure::	N/A
Total Drawing Sheets::	15
Small Entity::	No
Petition Included?::	No
Secrecy Order in Parent Appl.?::	No

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Fax:: (970) 224-3175  
Electronic Mail:: intentionally left blank

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**Continuity Information**

None

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Dated this 2 day of March, 2004.

Respectfully Submitted,  
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